IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	MUHRER *et al.*
Title:	PHARMACEUTICAL COMPOSITIONS
Appl. No.:	10/593401
International Filing Date:	3/22/2005
371(c) Date:	11/13/2006
Examiner:	Mina HAGHIGHATIAN
Art Unit:	1616
Confirmation Number:	2784

AMENDMENT AND REPLY UNDER 37 CFR 1.111

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Examiner Haghighatian:

This communication is responsive to the Non-Final Office Action dated July 21, 2010, concerning the above-referenced patent application. This communication accompanies a petition for a one-month extension of time, and associated fee, to make this communication timely.

Applicant does not believe that any additional fees are due, however the Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant

hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this document.

Amendments to the Drawings begin on page 6 of this document, and include the attached replacement drawing sheets.

Remarks/Arguments begin on page 7 of this document.

Please amend the application as follows:

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Previously Presented) A process for micronization of a pharmaceutically active agent comprising the steps of:
   (a) suspending the pharmaceutically active agent in a gas propellant or in a compressed gas,
   (b) processing this suspension by high pressure homogenization, and
   (c) obtaining dry powder upon depressurization.

2. (Previously Presented) A process for micronization of a pharmaceutically active agent comprising the steps of:
   (a) suspending the pharmaceutically active agent in a gas propellant,
   (b) processing this suspension by high pressure homogenization, and
   (c) obtaining a suspension of the micronized pharmaceutically active agent in the gas propellant.

3. (Previously Presented) The process according to claim 1 wherein the pharmaceutically active agent micronized by said process has an average particle size between about 0.1 and about 7.0 micrometers.

4. (Previously Presented) The process according to claim 1 wherein the pharmaceutically active agent micronized by said process has an average particle size of from about 0.5 to about 5.0 micrometers.

5. (Previously Presented) The process according to claim 1 wherein the suspension formed by the pharmaceutically active agent and the compressed gas or gas propellant comprises one or more pharmaceutically acceptable excipient.

6. (Previously Presented) The process according to claim 1 wherein the pharmaceutically active agent is poorly soluble in water and/or chemically or thermally unstable.

7. (Currently Amended) The process according to claim 1 wherein the pharmaceutically active agent comprises~~is chosen from~~ at least one of pimecrolimus (33-Epichloro-33-desoxy-ascomycin), 5-[(R)-2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-(1H)-quinolin-2-one, 3-methylthiophene-2-carboxylic acid (6S,9R,10S,11S,13S,16R,17R)- 9-chloro-6-fluoro-11-hydroxy-17-methoxycarbonyl-10,13,16-trimethyl-3-oxo- 6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta-[α]phenanthren-17-yl ester, N-benzoylstaurosporine, oxcarbazepine, carbamazepine, 1-(2,6-Difluoro- benzyl)-1H-[1,2,3]triazole-4-carboxylic acid amide, cox-2 inhibitors, pyrimidylalaminobenzamides, camptothecin derivatives, proteins, peptides, vitamins, steroids, bronchodilators.

8. (Currently Amended) The process according to claim 1 wherein the compressed gas comprises~~is chosen from~~ at least one of carbon dioxide, nitrogen, dimethyl ether, ethane, propane and butane.

9. (Previously Presented) The process according to claim 1 wherein the compressed gas is an HFA propellant qualified for human use.

10. (Previously Presented) The process according to claim 1 wherein the compressed gas is chosen from at least one of HFA134a and HFA227.

11. (Currently Amended) The process according to claim 5 wherein the pharmaceutically active excipient comprises~~is chosen from~~ at least one of surfactant, carrier and lubricant.

12. (Currently Amended) The process according to claim 11 wherein the surfactant comprises~~is chosen from~~ at least one of acetylated monoglycerides, perfluorocarboxylic acid, polyethylene glycol (PEG) sterol esters, polyethylene oxide sorbitan fatty acid esters, sorbitan esters, sorbitan mono laureate, sorbitan mono oleate, sorbitan tri oleate, sorbitan mono palmitate, propylene glycol and oleic acid.

13. (Previously Presented) The process according to claim 1 wherein the suspension of the pharmaceutically active agent in a gas propellant or compressed gas is processed by homogenization using static geometries.

14. (Previously Presented) The process according to claim 1 wherein the suspension of the pharmaceutically active agent in a gas propellant or compressed gas is processed by homogenization using a dynamic valve.

15. (Previously Presented) The process according to claim 1 wherein the suspension of the pharmaceutically active agent and the compressed gas or gas propellant is formed in a first stirred vessel and stored in a second stirred vessel after the micronization process.

16. (Previously Presented) A micronized pharmaceutically active agent obtained by the process of claim 1.

17. (Previously Presented) A pharmaceutical composition comprising the micronized pharmaceutically active agent of claim 16 and pharmaceutically acceptable excipients.

18. (Original) A package comprising a composition according to claim 17 and instructions to use.

19. (Currently Amended) A process according to claim 1 wherein said micronized pharmaceutically active agent is <u>filled directly to</u> ~~prepared in situ in~~ an inhalation device.

20-22. (Canceled)

23. (New) A process according to claim 2 wherein said micronized pharmaceutically active agent is filled directly to an inhalation device.

Amendments to the Drawings:

The drawing sheet or sheets attached in connection with the above-identified application containing FIGs. 2 and 3 are being presented as a replacement formal drawing sheet or sheets to be substituted for the previously submitted drawing sheet or sheets. Replacement FIGs. 2 and 3 are presented merely to clarify the text. No new matter has been added.

REMARKS

By the present communication, claims 7, 8, 11, 12 and 19 are amended, claim 22 canceled, and new claim 23 added. The amended and new claim language is supported by the international application as filed, including but not limited to original claim 19 and paragraphs 10, 11, 13-15, 20, 33-36 in the published application (US 2008/0026981). After entry of this amendment, claims 1-19 and 23 are pending and under examination in this application.

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

In the Office Action, Figures 2 and 3 have been objected to as not clear. Appended to this communication are replacement Figures 2 and 3 which Applicant believes to be satisfactory for printing and publication, thereby overcoming the grounds for this objection.

Claim 19 stands rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner asserts that claim 19 is related to a "process taking place in situ in an inhalation device, which only correspond in some undefined way to specifically instantly disclosed process." Applicant respectfully traverses this rejection.

While Applicant believes the Examiner has misconstrued claim 19 to require the micronization process to take place inside the inhalation device rather than in situ, solely to expedite prosecution, Applicant has amended claim 19 to recite the claimed invention with greater particularity. As amended, claim 19 recites that micronized pharmaceutically active agent is filled directly to an inhalation device. Basis for this amendment may be found at least at paragraph 34 and 35 of the application. Moreover, the extensive description of the process at paragraphs 23-35 make clear that

> the suspension of the pharmaceutically active agent in the propellant or compressed gas may be micronized in a single step process avoiding the need for any additional post-processing steps. Upon depressurization of the compressed gas or the propellant dry powder of the pharmaceutically active agent is obtained which may

> be used for inhalation formulation without any further processing. (paragraph 35)

Because the micronized pharmaceutically active agent may be used for dry powder inhaler formulations without further processing and because the suspension of micronized pharmaceutically active agent may be filled directly into suitable inhalation devices, Applicants submit the application contains ample written description for the claimed process. For the same reasons, Applicant submits that new claim 23 also finds support in the application as filed. Accordingly, Applicant requests that the rejection be withdrawn and the application moved toward issuance.

Claims 1-19 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description for the phrase, "gas propellant." In particular, the Examiner asserts that the phrase "gas propellant" is not supported by the specification as originally filed, and constitutes new matter. Applicant respectfully traverses this rejection.

Applicant submits that the term "gas propellant" is not new matter and is fully supported by the specification as filed. Applicant directs the Examiner's attention to paragraph 21 of the published specification (U.S. Pat. Pub. 2008/0026981), emphasis added:

> Another class of *compressed gases are propellants*, including hydrofluoroalkanes (HFA) e.g. 1,1,1,2-tetrafluoroethane (HFA 134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA 227). HFA 134a and HFA 227 are qualified for human use, and in contrast to chlorofluorocarbon (CFC) propellants they have no depleting effect on the ozone layer. Further examples of hydrofluoroalkane propellants are perfluoroethane, monochlorodifluoromethane and difluoroethane. A combination of propellants may also be used.

Based on this disclosure, the person of ordinary skill in the art will readily understand that propellants are a species of compressed gases. The application further makes clear that the propellants and compressed gasses are used in the gas state rather than the liquid state. First, all of the materials listed as propellants, *e.g.* hydrofluoroalkanes (HFA) e.g. 1,1,1,2-tetrafluoroethane (HFA 134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA 227), are in fact gasses. Second, the application discloses that the present methods utilize compressed gas

suspensions of particles (see, e.g., paragraphs 19, 22, 23, and 25) and distinguishes these methods from conventional homogenization processes that require formation of a suspension of solids or liquids in a *liquid*. *Id.*, paragraph 24. Hence, to avoid confusion with liquid propellants, and identify those propellants which are compressed gases, Applicant's claims recite the term "gas propellant." In view of the cited disclosures in the specification, Applicant submits that one of skill in the art would readily acknowledge that the term "gas propellant" is fully supported by the application as filed. As such, Applicant respectfully requests withdrawal of this ground of rejection.

Applicant traverses the rejection of claims 7, 8, 11, and 12 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for reciting an improper Markush group. Applicant notes that as amended, claims 7, 8, 11, and 12 recite "...comprises at least one of..." Support for this amendment is found in the claims as filed and at least at paragraphs 10, 11, 13-15 and 20. Applicant submits that the claims as written are clear and requests withdrawal of the rejection.

35 U.S.C. § 103(a)

Claims 1-19 and 22 stand rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over U.S. Pat. No. 6,135,628, issued to DeStefano *et al*. Applicant respectfully traverses this rejection.

Applicant asserts that DeStefano fails to teach or suggest each and every element of the presently claimed invention, and the Examiner has failed to point to any reason for the person of ordinary skill in the art to modify the reference to provide for the missing elements. Accordingly, the reference cannot be found to render the claims obvious. In particular, DeStefano fails to teach or suggest a micronization method in which a pharmaceutically active agent is suspended in a gas propellant or compressed gas.

According to claim 1, the presently claimed invention is directed to:

> A process for micronization of a pharmaceutically active agent comprising the steps of:

> (a) suspending the pharmaceutically active agent in a gas propellant or in a compressed gas,
>
> (b) processing this suspension by high pressure homogenization, and
>
> (c) obtaining dry powder upon depressurization.

Similarly, claim 2 recites a process for micronization by suspending the pharmaceutically active agent in a gas propellant. Both independent claims are therefore directed to suspending the agent in either a *gas* propellant or a compressed *gas*. Thus, the suspending medium is a gas but is not a liquefied gas. DeStefano fails to teach or suggest the suspension of an active pharmaceutical agent in such a gas.

DeStefano is directed to the use of liquid propellants for suspending/dissolving pharmaceutical agents as an aerosol formulation. DeStefano teaches that while an "aerosol" is a gaseous suspension of fine solid or liquid particles, an "aerosol formulation" is defined as "one which comprises a solution or suspension of an active ingredient in a liquid which consists of a propellant and any necessary solvent or surfactant." Col. 1, lines 19-23 (emphasis added). Hence, whenever DeStefano mentions "aerosol formulation" it is a reference to the liquid, not gaseous, form of the composition.

DeStefano discloses that "homogenization of a formulation comprising a low boiling HFA (hydrofluorocarbon alkane) must either be carried out at elevated pressure or reduced temperature because the low boiling HFA would otherwise evaporate." Col. 3, lines 1-8. Moreover, DeStefano further discloses that "rotor/stator homogenizers do not presently exist which are adapted to operate under sufficient pressure to prevent the volatilization of a low boiling constituent, such as a propellant." Col. 3, lines 10-13. DeStefano solves this problem by providing a "pressurizable system for homogenizing aerosol formulations." Col. 3, lines 40-42. Clearly, DeStefano is concerned with avoiding the gases form of HFA solvents or he would not mention the volatilization and evaporation of HFA solvents.

DeStefano also adds that "[o]nce all of the components of the aerosol formulation are in the mixing vessel 10 and the mixing vessel is pressurized to about 70-80 psi, the aerosol formulation is ready for mixing, homogenization and micronization." Col. 7, lines 1-6.

Moreover, the note to the table listing formulation components in column 7 states that the quantity of low boiling solvent (1,1,1,2,3,3,3-heptafluoropropane) used includes some to make up for losses during filling as the "liquid bulk suspension" is depleted. The only suspension in the system is that of the pharmaceutically active ingredient and surfactant in the low boiling HFA. That the suspension was in liquid and bulk form, suggests that this is the form of composition in the mixing vessel.

Taken together, the above statements clearly convey to the skilled artisan that the aerosol formulation remains liquid throughout the DeStefano system and not just within the homogenizer. As such, DeStefano fundamentally differs from the claimed invention in suspending the pharmaceutically active ingredient in a liquid propellant rather than a gas propellant or compressed gas. There is simply no suggestion that a gas suspension of the agent to be micronized should or could be used rather than a liquid suspension.

Because DeStefano does not teach or suggest the use of a compressed gas or gas propellant for suspension of an active agent, DeStefano cannot be found to render the presently claimed invention obvious. Accordingly, Applicant respectfully requests withdrawal of this rejection and that that application be allowed to proceed to issuance.

Claims 1-19 and 22 stand rejected under 35 U.S.C. § 103(a), as being unpatentable over U.S. Pat. No. 6,228,346, issued to Zhang *et al.* in view of WO 0025746, by Bernini *et al.* Applicant respectfully traverses this rejection.

Zhang describes methods for preparing an aerosol formulation through the use of "a special propellant mixture…so as to micronize the drugs for pulmonary application. This propellant mixture is present in the *subcritical state*…" Col. 3, lines 26-30, emphasis added. The skilled artisan understands that the subcritical state for a gas is the liquid state. In fact, the examples describe that the pharmaceutical compound is dissolved in a liquid mixture by maintaining vapor pressure of 5 to 20 bar. Thus, like DeStefano above, Zhang is direct to suspension of the pharmaceutically active agent in a liquid medium to prepare the aerosol

formulation, and Bernini fails to cure this deficiency with respect to the presently claimed invention.

Bernini is directed to the preparation of particle suspensions for use in formulations for aerosol inhalation. *See* page 2, lines 13-15. This is accomplished using a turboemulsifier, which includes a containment vessel equipped with magnetic stirring and a high potency turbine system for homogenizing the suspension. *See* page 2, lines 15-26. Bernini then goes on to describe that the "process includes a first step wherein an *aqueous solution* which constitutes the carrier is dispersed in a turboemulsifier apparatus." *Id.* In a preferred embodiment, the drug is dispersed in the aqueous phase and then is subject to additional homogenization under high pressure. *See* page 3, lines 12-15. Thus, Bernini, like Zhang, and DeStefano above, is direct to suspension in a liquid medium to prepare the aerosol formulation.

In summary, none of the cited references teach or suggest the use of compressed gas or gas propellant for the suspension of a pharmaceutically active agent processing this suspension by high pressure homogenization. Accordingly, alone or in combination, the references fail to teach or suggest each and every element of the claimed invention. Applicant therefore respectfully requests withdrawal of the pending rejections.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. If any issues remain to be addressed in view of the present response, the Examiner is invited to contact the undersigned by telephone if to advance the prosecution of the present application.

Respectfully submitted,

Date November 11, 2010

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